REMARKS

This Response is filed in connection with the Office Action mailed August 10, 2004. Claims 1 to 70 are pending. Claims 1 to 32 and 56 to 70 stand withdrawn from consideration as directed to non-elected subject matter. Claims 56 to 70 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 71 to 86, based upon claims 31 to 55 of the elected invention, have been added. Accordingly, upon entry of the Response, claims 31 to 55 and 71 to 86 are under consideration.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification or were made to address an informality. In particular, the amendment reciting "insulin" is supported, for example, by claim 45, as originally filed. The amendment reciting "gut or gastrointestinal" mucosal cells is supported, for example, at page 5, line 27, to page 6, line 1. The amendment to recite "gut endocrine promoter" is supported, for example, by claim 43, as originally filed. The amendment reciting "an amount of sugar, carbohydrate, starch, polypeptide, amino acid or fat" is supported, for example, by claim 41, as originally filed, at page 15, lines 9-12; and page 16, lines 1-6. The amendment to recite that "the gut endocrine promoter functional variant or subsequence retains all or a part of non-variant or full-length gut endocrine promoter expression function" is supported, for example, at page 12, line 28, to page 13, line 12; at page 16, lines 18-25; and at page 17, lines 3-9. The amendment reciting "the transformed gut or gastrointestinal mucosal tissue cells " was made in order to more clearly indicate that the insulin or leptin is produced by the transformed gut or gastrointestinal mucosal tissue cells. The amendment to claim 43 to depend from claim 31 instead of claim 42, was necessitated by the cancellation of claim 42. Thus, as the claim amendments are supported by the specification or were made to address an informality, no new matter has been added. Furthermore, the amendments place in the claims in better form for allowance or consideration on appeal. Entry of the amendments is therefore respectfully requested.

Regarding the New Claims

New claims 71 to 86 substantially parallel the subject matter of claims 31 to 55 prior to entry of the claim amendments set forth herein. Claims 71 to 86 are therefore supported by originally filed claims 31 to 55 and, therefore, do not add new matter. Furthermore, the new claims place the claims in better form for allowance or consideration on appeal. Entry of claims 71 to 86 is therefore respectfully requested.

REJECTIONS UNDER 35 U.S.C. §112

The rejection of claims 31 to 55, 43 and 44 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description, is respectfully traversed. Allegedly, "the written description requirement is not satisfied for the claimed genus" of " nutrients." Allegedly, "the specification of record has not described which variants or subsequences of gut endocrine promoters possess the biological activity of a gut endocrine promoter." [Office Action, page 4]

The specification adequately describes claims 31 to 55, 43 and 44. Applicants respectfully point out that in order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the specification need only apprise the skilled artisan of the invention in sufficient detail to demonstrate Applicants had possession of the invention. Possession may be shown by "any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). An adequate written description does not require the disclosure of every species encompassed by the claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976). In *Lilly*, the court explained "every species in a genus need not be described in order that a genus meet the written description requirement." *Id.* (*citing Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988)). Thus, a description of every nutrient capable of inducing production of a protein, and a description of every gut endocrine promoter variant or subsequence, is not necessary in order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

For nutrients, in view of the specification and knowledge in the art, one skilled in the art would be apprised of a variety of nutrients that induce production of a protein, either by increased expression or secretion. For example, as disclosed in the specification, the skilled artisan would know that a variety of nutrients induce production of a protein. For example, the

specification discloses that glucose can increase expression of an operably linked nucleic acid (see, for example, page 13, lines 21-24; and page 17, lines 17-25). The specification discloses that Vitamin D is a nutrient that can regulate expression, for example, through a Vitamin D response element (page 17, lines 26-28). The specification discloses that secretion of a protein can be induced by a nutrient (see, for example, page 19, lines 14-19). Various nutrients, including sugars, carbohydrates, starches, fats, peptides and amino acids, that induce protein expression or secretion are known. Consequently, in view of the specification and knowledge in the art, the skilled artisan would know of a variety of nutrients that induce production of a protein.

Nevertheless, without acquiescing to the propriety of the rejection and solely in order to further prosecution of the application, the claims have been amended to recite that a "sugar, carbohydrate, starch, polypeptide, amino acid or fat" induces production of the insulin or leptin. Each of the recited nutrients can induce production of a protein, by virtue of either increased gut endocrine promoter expression or increased gut endocrine promoter secretion. Consequently, the ground for rejection of claims 31 to 55 must properly be withdrawn.

As to claims 43 and 44 and an adequate description of gut endocrine promoter variants and subsequences, Applicants maintain that in view of the guidance in the specification and knowledge in the art regarding the sequence of gut endocrine promoters and the sequence regions that are or are likely to participate in expression function, the skilled artisan would know of a variety of gut endocrine promoter or enhancer regions that could be varied or deleted without destroying expression function. Consequently, because the skilled artisan would know of a variety of gut endocrine promoter and enhancer sequences that could be varied or deleted, the skilled artisan would know of numerous gut endocrine promoter and enhancer variants and subsequences that retain gut endocrine promoter expression activity. Further in this regard, claims 43 and 44 have been amended to more clearly indicate that the variants and subsequences of gut endocrine promoters "retains all or a part of non-variant or full-length gut endocrine promoter expression function."

As previously pointed out in the record, the specification discloses a number of gut endocrine promoters. Specific non-limiting examples include GIP promoter, secretin promoter, gastrin promoter, cholecystokinin (CCK) promoter, proglucagon promoter, chromogranin A

promoter and chromogranin B promoter. The nucleotide sequences of these and other gut endocrine promoters are disclosed by the specification or known in the art.

Furthermore, the specification teaches various sequence regions of gut endocrine promoters that participate in expression function. Moreover, various sequence regions of gut endocrine promoters that participate in expression function are known in the art. Thus, because a variety of sequence regions that mediate gut endocrine promoter expression function are known the skilled artisan would know of sequence regions of gut endocrine promoters that could be varied or deleted without destroying expression function to the skilled artisan. Consequently, the skilled artisan would know of a number of gut endocrine promoter variants and subsequences having function, i.e., that retain at least a part of non-variant or full length gut-endocrine promoter expression function.

To illustrate this point, each of the particular gut endocrine promoters disclosed in the specification contain a number of structurally conserved sequence regions such that the skilled artisan would know where point mutations or deletions could be introduced without destroying expression function. As an example, GIP nucleic acid sequence is disclosed in the specification, and the GIP promoter has two TATA boxes and two CCAAT-like boxes, potential AP-1 and AP-2 sites, a cAMP response element, a potential insulin-response element located upstream of the putative transcription start site and two GATA binding motifs. TATA boxes and/or CCAAT boxes appear frequently in promoters, and are known to be important for promoter expression function generally. The functions of these sequence regions in GIP promoter can be inferred based upon their function in other promoters. In addition, mutations in the distal and proximal GAT motifs reduced GIP promoter activity 90% and 35%, respectively, demonstrating their role in GIP promoter expression function.

A variety of GIP variants and subsequences have also been produced revealing sequence regions that are important for GIP promoter expression function. For example, a sequence region between –180 and +14 of human GIP promoter conferred basal promoter activity in an insulinoma cell line. The first 193bp upstream of the transcription initiation site of the *rat* GIP promoter was able to direct approximately the same level of expression as a 943bp promoter fragment in STC-1 cells. Thus, in view of this knowledge a rat GIP sequence from about -180 and +14 or about the first 193bp upstream of the transcription initiation site would have at least partial expression function and, as such, would be a subsequence.

DNase I footprinting and gel mobility shift assays identified one near-canonical and one atypical cAMP response elements (CRE) at positions –351 (AGACGTGA) and –158 (TCACCAAT), respectively of the *human* GIP promoter. Both CRE sites are essential for basal promoter activity. Thus, because these CRE's are important for human GIP promoter expression function the skilled artisan would know that nucleotides outside of the CRE's could be mutated or deleted without destroying human GIP promoter expression function.

In view of the fact that sequence regions that mediate GIP promoter expression function are known or can be inferred based upon homology to sequences of other promoters, that sequence regions that can confer GIP promoter expression function are also known, the skilled artisan would know GIP promoter sequence regions that could be varied or deleted without destroying GIP expression function. Consequently, the skilled artisan would also know of a number of GIP promoter variants and subsequences that would retain at least a part of native GIP promoter expression function.

Given the fact that a GIP promoter of 2.5 Kb in length displays expression function, clearly a significant number of GIP promoter variants and subsequences that retain at least a part of the GIP expression function would be known. In this regard, it cannot reasonably be argued that over the entire sequence length of a given gut endocrine promoter, such as a 2500 nucleotide GIP promoter, that the skilled artisan, knowing the structure and function of various sequence regions of GIP promoter discussed above and in the record, would not know where to introduce one or a few point mutations or deletions to produce a GIP promoter variant or subsequence that retained at least a part of GIP promoter expression function.

Further in this regard, the Patent Office asserts that the specification "only" describes a few number of variants or subsequences having reduced activity (page 5, second paragraph). With all due respect, the fact that such gut endocrine promoter sequences do retain partial expression function is precisely the point and corroborates that the skilled artisan would know of a variety of gut endocrine promoter variants and subsequences that retain at least a part of expression function of non-variant or full-length gut endocrine promoter. Furthermore, Applicants again remind the Patent Office out that the law does <u>not</u> require the actual disclosure of a particular number of variants and subsequences to show possession: rather, Applicants need only provide "any description of sufficient, relevant, identifying characteristics so long as a

person skilled in the art would recognize that the inventor had possession of the claimed invention."

The Patent Office also asserts that there is no relationship between the structure of any gut endocrine promoter and the claimed variants or subsequences (page 5, second paragraph; and page 6, second paragraph). To the contrary, the skilled artisan would know that in order to retain at least partial expression function of non-variant or full-length gut endocrine promoters, the sequence of gut endocrine promoter variants and subsequences will share substantial sequence homology with non-variant or full-length gut endocrine promoter. For example, a variant or subsequence of GIP promoter will share substantial sequence homology with the native GIP promoter in order to retain at least partial expression function of native GIP promoter. Thus, although there will be some sequence variation between different gut endocrine promoter variants and subsequences and non-variant or full-length counterparts, the skilled artisan would know that the majority of nucleic acid residues for a given promoter variant or subsequence and its native counterpart will be identical. Consequently, there is no factual support for the assertion that the skilled artisan would not know the relationship between structure of a gut endocrine promoter and variants or subsequences of that promoter that retain a part of expression function.

The Patent Office appears to have taken the position that because a significant number of such sequences have not been reduced to working examples that the skilled artisan would not know of a representative number of gut endocrine promoter variants and subsequences. However, once again, the law does not require the disclosure of a certain number or even a large number of working examples in order to satisfy the written description requirement under §112, first paragraph. Here, the guidance in the specification and the knowledge in the art regarding gut endocrine promoter sequences and sequence regions important for expression function are more than adequate for the skilled artisan to be apprised of numerous gut endocrine promoter variants and subsequences that retain all or a part of non-variant or full-length gut endocrine promoter expression function. Again, 1) the nucleic acid sequence of a number of gut endocrine promoters are known; 2) the specification teaches specific sequence regions of various gut endocrine promoters that mediate expression function; 3) the sequence regions of various gut endocrine promoters that mediate expression function are known in the art; and 4) sequences that contribute to promoter expression function are known in the art generally such that

corresponding sequences present in gut endocrine promoters are likely to share a corresponding function.

The same analysis is applicable to other gut endocrine promoters and enhancers. Analogous to GIP promoter, the skilled artisan would have known the nucleic acid sequence and sequence regions that do or are likely to mediate expression function of a given promoter or enhancer. Consequently, the skilled artisan would also know variants and subsequences of that gut endocrine promoter or enhancer that retains at least a part of expression function of that gut endocrine promoter or enhancer.

For secretin, promoter sequences between 174 and 53 bp upstream from the secretin transcriptional start site confer maximal expression. Within this sequence region there are four cis-acting elements characterized in transient expression assays. Thus, the skilled artisan knows that the 174 and 53 bp region is sufficient to confer expression function and, furthermore, that deleting the four cis acting elements within this region would likely destroy secretin promoter expression function. The BETA2 protein binds to the E box in the secretin gene and interacts with p300 to activate secretin transcription. A 1.6kb 5' flanking sequence of rat secretin gene conferred tissue-specific, developmentally regulated expression in mice. Thus, the skilled artisan would know that the E box contributes to secreting promoter expression function, and that a 1.6kb 5' flanking sequence of rat secretin gene is sufficient to confer expression function.

For gastrin, transcription was shown to be increased by epidermal growth factor and an EGF response element (gERE) is located between -54 to -68 bp 5' of the transcription initiation site of human gastrin promoter. Gastrin transcription in islet cells is activated by a cis-regulatory sequence containing a RAP1-like binding site. Sp transcription factor members Sp1 and Sp3, which have been identified as important for activating a number of promoters via cis-acting elements, bind to this RAP-1 site. A positive cis-regulatory element (CACC) is located from position -109 to -100 bp. RIN ZF, a member of the Cys2-His2 zinc finger family, binds to this CACC element and regulates gastrin gene expression. Thus, in view of the foregoing, a variety of sequence regions within gastrin promoter that have and are likely to have a role in expression function would be known. Consequently, the skilled artisan would also know of a variety of gastrin promoter variants and subsequences that retain at least a part of secretin promoter expression function.

Cholecystokinin (CCK) gene region from –100 to –20 relative to the transcriptional start site contains an E-box element (-97 to –92 CANNTG), a combined CRE/TRE element (-79 to –73), a GC-rich box (-39 to –32) and a TATA-box. Since each of these sequence regions are present in other promoters and are known to be important for expression function, the skilled artisan would know that such sequences within CCK promoter are likely to have a role in expression function. Consequently, the skilled artisan would know of a variety of CCK promoter variants and subsequences that retain at least a part of CCK promoter expression function.

The proglucagon gene spans approximately 10kb and 300 base pairs of the 5'-flanking region of rat proglucagon gene conferred specific expression in islet cell lines. Three transcriptional control elements, G2 (-181 to –202) and G3 (-265 to –286), each displayed enhancer activity in alpha cells. The third control element, G1 proximal promoter element (-52 to –100), exhibited low intrinsic transcriptional activity but was important for specific expression in alpha cells. A composite control element, G4, located upstream of G1 between nucleotides -100 and –140, functions as an islet-specific activator in both glucagon- and insulin-producing cells and is inactive in non-islet cells. A cyclic-AMP responsive element (CRE) is also present at positions -291 to –298. Thus, a variety of sequence elements within proglucagon promoter that have and are likely to have a role in expression function would be known. Consequently, the skilled artisan would also know of a variety of proglucagon promoter variants and subsequences that retain at least a part of proglucagon promoter expression function.

Chromogranin A gene has a glucocorticoid response element located at position -583 to -597 bp, which confers glucocorticoid regulation. An Sp1/Egr-1 site spans -88 to -77 base pairs (bp) and a cyclic AMP-responsive element (CRE) is located at -71 to -64 bp; both are important for gastrin-dependent chromogranin A activation. Gastrin regulates Sp1 binding to the chromogranin A -88 to -77 bp promoter element, as well as CREB binding to the chromogranin A consensus motif at -71 to -64 bp. Thus, a variety of sequence elements within chromogranin A promoter that have and are likely to have a role in expression function would be known. Consequently, the skilled artisan would also know of a variety of chromogranin A promoter variants and subsequences that retain at least a part of chromogranin A promoter expression function.

Chromogranin B gene promoter is GC-rich and contains a CATAA motif, a cAMP-responsive element and an Sp1 binding site. Neuroendocrine cell type-specific expression

activity is conferred by proximal chromogranin B promoter, from -216 to -91 bp, which contains an E box (at -206 bp-201 bp), four G/C-rich regions (at -196 bp-191 bp, -134 bp -127 bp, -125 bp -117 bp, and -115 bp -110 bp), and a cAMP response element (CRE; at -102 bp -95 bp). Thus, a variety of sequence elements within chromogranin B promoter that have a role in expression function would be known. Consequently, the skilled artisan would also know of a variety of chromogranin B promoter variants and subsequences that retain at least a part of chromogranin B promoter expression function.

In sum, the skilled artisan would have known 1) the nucleic acid sequence of a variety of gut endocrine promoters; 2) specific sequence regions known to mediate gut endocrine promoter expression function; 3) specific sequence regions inferred to mediate gut endocrine promoter expression function, based upon homology to sequence regions of other promoters having expression function; and 4) that gut endocrine promoter variants and subsequences would share significant sequence homology with the native counterpart promoter in order to retain all or a part of expression function. Thus, the skilled artisan would know nucleotides that could be substituted or deleted without destroying gut endocrine promoter or enhancer activity and, therefore, a large number of gut endocrine promoter and enhancer variants and subsequences that retain at least a part of non-variant or full-length gut endocrine promoter expression function. Consequently, as gut endocrine promoters and enhancers having variations or deletions that retain at least a part of non-variant or full-length gut endocrine promoter expression function would be known to one skilled in the art, an adequate written description for claims 43 and 44 is provided. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description, be withdrawn.

The rejection of claims 31 to 55 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner has maintained the rejection.

Claims 31 to 55 and 71 to 86 are adequately enabled. Here, the grounds for rejection relate solely to an alleged "unpredictability of the gene therapy art." [Office Action, page 5]

Applicants reiterate that this rejection is improper since gene therapy is not required in order to practice claims 31 to 55 and 71 to 86. Here, claims 31 to 55 and 71 to 86 do not recite a step of transforming mucosal cells but, rather, "contacting mucosal tissue cells in the subject transformed with a polynucleotide comprising an expression control element in operable linkage

with a nucleic acid encoding the therapeutic protein with a nutrient that induces production of the protein in an amount effective to treat the disorder." Furthermore, Applicants have submitted evidence herewith and in the record that cells can be transformed with a polynucleotide comprising an expression control element in operable linkage with a nucleic acid encoding a protein *in vivo* by injection or by luminal incubation, and that therapeutically relevant levels of various proteins (e.g., insulin, SEAP) can be produced (see, for example, Exhibits 1 and 2, filed June 16, 2004, and Exhibit AA, submitted herewith). In this regard, Applicants respectfully remind the Patent Office that the failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. §112. *Spectra-Physics v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir., *cert. denied*, 484 U.S. 954 (1987)- citing *In re Glass*, 492 F.2d 1228, 1233, "[n]onenablement is the failure to disclose *any* mode and does not depend on the applicant advocating a particular embodiment or method for making the invention.") Moreover, other investigators have demonstrated that at the time of the invention polynucleotides can be introduced into cells *in vivo* and the encoded proteins expressed at therapeutically relevant levels (as an example, Factor IX).

Thus, in view of the guidance in the specification, the skilled artisan could transform cells *in vivo* using various techniques without undue experimentation. As such, the grounds for rejection under 35 U.S.C. §112, first paragraph, relating to enabling gene therapy are improper and must be withdrawn.

Nevertheless, solely in order to further prosecution of the subject application and without acquiescing to the propriety of the rejection, the claims have been amended to recite that the therapeutic protein comprises "insulin." New claims 71 to 86 parallel the amended claims, with the therapeutic protein comprising "leptin."

Applicants previously submitted Exhibit A, a sworn Declaration under 37 C.F.R. §1.132 and accompanying Figures 1-11, executed by Dr. Timothy Kieffer. Exhibit A provided animal studies in which a therapeutic protein (leptin) from transplanted gut cells (GTC-1) was produced in animals in an amount effective to treat obesity and normalize glucose levels. The data in previously submitted Exhibit A therefore corroborates that a polynucleotide encoding a protein, such as leptin, can be introduced into mucosal tissue cells and sufficient protein produced *in vivo* in an animal in amounts effective to treat the disorder.

To corroborate that *in vivo* transformed mucosal cells produce therapeutically relevant levels of proteins, Exhibit 1 and 2, a sworn Declaration under 37 C.F.R. §1.132 executed by Dr. Anthony Cheung and accompanying Figures 1-4, respectively, were previously submitted. Previously submitted Exhibits 1 and 2 included data indicating that levels of insulin produced by *in vivo* transformation of mucosal cells with insulin gene are sufficient to reduce glucose in animals. In addition to insulin, red fluorescent protein (DsRed) and green fluorescent protein (GFP) were also stably introduced into mucosal tissue of rats using *in vivo* gene delivery methods with AAV and FIV vectors.

As additional corroboration that polynucleotides encoding proteins can be introduced into mucosal cells *in vivo*, and that therapeutically relevant levels of protein produced in animals, submitted herewith is a sworn Declaration under 37 C.F.R. §1.132 by Dr. Anthony Cheung, Exhibit AA and accompanying Figures 1 and 2. Exhibit AA and Figures 1 and 2 include data indicating that 1) a single administration of a polynucleotide encoding insulin into gut lumen *in vivo* results in long term production of insulin; 2) insulin production following administration *in vivo* is at therapeutically relevant levels in animals; 3) insulin was produced in amounts effective to protect animals from death caused by streptozocin (STZ), which renders the animals unable to produce insulin; and 4) other gut endocrine promoters can drive expression of polynucleotides encoding proteins produced *in vivo* in amounts that are therapeutically relevant.

In brief, two FIV vectors, with either a human insulin gene or secreted embryonic alkaline phosphatase (SEAP) gene, driven by a rat GIP promoter or a mouse chromagranin A promoter, respectively, were constructed (Exhibit AA, paragraph 6). FIV vectors harboring the insulin or SEAP gene were delivered to gut mucosal tissue of mice *in vivo* by a single injection into the lumen of duodenum (Exhibit AA, paragraph 7). Blood C-peptide and SEAP levels were determined weekly in animals up to 150 days after vector delivery (Exhibit AA, paragraph 8).

Approximately 50 days after delivery, plasma human C-peptide levels increased and remained at an average of about 15 pM (Exhibit AA, paragraph 10, Figure 1, attached). C-peptide is released from insulin producing cells in amounts equal to insulin. Approximately 120 days after delivery human C-peptide levels began to decrease, presumably due to immune clearance of the human insulin. Nevertheless, even 150 days after vector delivery, three of the five animals originally delivered the insulin vector continued producing human C-peptide (Exhibit AA, paragraph 10). Dr. Cheung therefore concludes that based upon the data, long term

production of insulin in the bloodstream at therapeutically relevant levels can be achieved by a single *in vivo* administration of vector harboring polynucleotide encoding insulin into gut or gastrointestinal mucosal tissue.

Mice that continued producing insulin 150 days after delivery and mice that did not produce detectable C-peptide were injected with STZ at a dose that induces diabetes due to destruction of insulin producing pancreatic β-cells. Mice that continued to produce insulin survived STZ- treatment whereas mice that did not died within 3 days of STZ treatment (Exhibit AA, paragraph 10, Figure 2). The data indicate that insulin delivered by a single administration of a nucleic acid encoding insulin to gut or gastrointestinal mucosal tissue cells *in vivo* is functional and is produced at therapeutic levels.

Mice delivered FIV vector carrying a mouse chromagranin A promoter driving SEAP expression, produced plasma levels of SEAP that remained relatively constant after day 10, and up until day 58 approximately 15 pg/ml, the end of the monitoring period (Exhibit AA, paragraph 12, Figure 2). Levels of circulating SEAP remained in the pM range, which is within the therapeutic range for insulin and other proteins.

Based upon the data in Exhibit AA and in the record, Dr. Cheung concludes that proteins in general can be produced at therapeutic levels *in vivo* with different promoters by delivering polynucleotide encoding protein into gut or gastrointestinal mucosal tissue cells *in vivo* (Exhibit AA, paragraph 13). Dr. Cheung also concludes that therapeutic levels of protein can be produced in animals over an extended period of time and with a single administration *in vivo*, and that proteins are produced within the therapeutic range using different promoters (Exhibit AA, paragraphs 13 and 14). Furthermore, Dr. Cheung concludes that transfer of polynucleotide encoding a protein into gut or gastrointestinal mucosal tissue cells *in vivo* and production of the protein at therapeutically relevant levels in animals would not require undue experimentation (Exhibit AA, paragraph 15).

In view of the foregoing data, that insulin and SEAP are produced at therapeutic levels for insulin and other proteins using different promoters, and in view of the data of record, that therapeutic levels of insulin and leptin can be expressed in animal mucosal cells transformed with a nucleic acid encoding insulin or leptin, and that different vectors can be used to deliver genes to animals *in vivo* and therapeutically relevant levels of protein produced in the animals,

claims 31 to 55 and 71 to 86 are adequately enabled. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 31 to 55 and 71 to 86 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

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